REMARKS

Claims 14, 24, and 29-60 were in this case. Claims 14 and 24 have been withdrawn from consideration and are canceled by this amendment. Claims 29-60 are rejected. New claims 61-63 which depend from claim 29 and which read on the elected species are added. Claims 29-63 are now under consideration in this case.

Oath/Declaration

The Inventors declaration filed in this case is alleged to be defective because of non-initialed and/or non-dated alterations. The undersigned has reviewed the declaration submitted and notes that inventor Kurt Vermeire added his post office address to the declaration and corrected the spelling of his town of residence on signing the declaration. Because these additions were made directly above inventor Kurt Vermeire's signature, it is believed that the declaration should be considered not to be defective.

In any event, if the Examiner still considers that the declaration is defective, Applicants respectfully request deferral of this requirement until one or more claims in this case are found allowable.

Amendment of the Claims

Claim 29 has been amended to correct several typographic errors. The word "steps" is rewritten as "step." The word "Optional" is rewritten as "optional." The second recitation of R in claim 29 has been replaced with "R'." The spelling of "ameliorated" and "suppression" has been corrected.

To improve clarity the word "about" in relation to numbers of carbon atoms is deleted, the phrase "C labeled with subscripts a-d" is rewritten as "C_a, C_b, C_d, and C_e, " and the word "includes" has been replaced with "is."

Claim 29 is amended to recite that the variables $a + d + e \geq 1$. This amendment is supported in the specification at page 5, lines 7 and 8.

Claim 29 is further amended to clarify the definition of optional substitution. Optional substitution is defined generally in the specification at page 6, lines 1-16 as being substitution by one or more charged, polar or nonpolar substituents. In claims 29, optional substitution is more specifically defined to encompass certain charged, polar and non-polar substituents which are listed on page 6. To improve clarity R groups associated with the polar and nonpolar have been renamed R' groups to avoid confusion with R groups defined in the definition of variable W in claim 29. In addition, the specification at page 4, lines 18-25, lists further possible substitution of aryl groups.

Claim 30 is amended to rewrite "alky" as "alkyl." Additionally, several recitations of the word "about" have been deleted.

Claim 60 has been amended to delete the words "such as."

New claims 61-63 have been added. New claim 61 is supported in the specification at page 6, lines 2-3. New claim 62 is supported in the specification at page 13, lines 6-7. New claim 63 is supported in as-filed claim 58.

The amendments do not add new matter to the specification.

The Rejections

1. Claims 29-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. A list of reasons is provided as follows:

a) Claims 29, 31-39, 41, 42 and 58-60 are vague and indefinite in that it is not known what is meant by an alkyl group "carrying a charged substituent". There is no indication in the claims what the counter ion would be.

b) Claim 29 is vague and indefinite in that it is not known what is meant by the capital letter in the fifth line on page 8, i.e., Optional. Capital letters are only to be used at the beginning of the claim and in variables for chemical cases.

c) Claims 29-60 are vague and indefinite in that it is not known what is meant by alky in the definition of R on page 8, line 8; page 8, line 3 of claim 30;.

d) Claims 29-60 are vague and indefinite in that it is not known what is meant by the two different definitions of R. R is defined on page 7, lines 11-14 and again on page 8, lines 8-9.

e) Claims 29-60 are vague and indefinite in that it is not known what is meant by "one or more polar groups" in the definition of the labeled "C" of the formula, i.e., page 8, line 15.

f) Claim 46 is vague and indefinite in that it is not known what is meant by the moiety -S02, which is a divalent moiety, however, there is only one point of attachment, and

g) Regarding claim 60, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

The claims have been amended to obviate the rejection with respect to paragraphs b, c, d, f and g, above. Applicants respectfully traverse the rejection with respect to paragraphs a and e above.

The word optional in claim 29 was inadvertently capitalized. This error has been corrected.

The word “alkyl” was misspelled as “alky” in claim 30. This error has been corrected.

The same variable R was inadvertently used in two different variable definitions. The second recitation of R in claim 29 has been amended to recite “R’” rather than “R” to correct this error.

An inadvertent error is corrected in claim 46 by replacing “-SO_2” with ‘-SO_2-“.

Claim 60 has been amended to delete the words "such as" which were objected to.

It is alleged that claims 29, 31-39, 41, 42 and 58-60 are vague and indefinite in that it is not known what is meant by an alkyl group "carrying a charged substituent". It is said that there is no indication in the claims what the counter ion would be. The phrase "substituted alkyl group carrying a charged substituent" refer to an alkyl group substituted with a charged group. The term "charged group" is understood in the art, particularly in view of the examples of charged groups which are given in the specification e.g., on page 4, line 1. With respect to counterions, the claim is directed to the use of compounds of the listed formula and pharmaceutically acceptable salts thereof. One of ordinary skill in the art understands that pharmaceutically acceptable salts include appropriate pharmaceutically acceptable counterions. A variety of such counterions are known in the art. Thus, the claim is not indefinite with respect to the term "charged substituent".

It is alleged that claims 29-60 are vague and indefinite in that it is not known what is meant by "one or more polar groups" in the definition of the labeled "C" of the formula, i.e., page 8, line 15. The term "polar group" is understood in the art, particularly in view of the examples of polar groups which are given in the specification e.g., on page 10, lines 6-10. Thus, the term "polar group" is understood in the art and is not indefinite.

The rejection of claims 29-60 continues with the following:

> Claims 29-60 are vague and indefinite in that the claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in determining which are the disorders capable of being treated by ameliorated by suppression of CD4+-T-cell-mediated immune response. Determining whether a given disease responds or does not respond to such an inhibitor will involve undue experimentation. Suppose that a given drug, which has inhibitor properties in vitro, when administered to a patient with a certain disease, does not produce a

favorable response. One cannot conclude that specific disease does not fall within this claim.

Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital -- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration cannot be predicted in advance. Should our drug be given as a bolus iv or in a time release po formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active in vitro, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related inhibitors must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of which are inhibitors in vitro, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property, which the second drug is capable. It is common for a drug, particularly in analgesics, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to affect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually precede linking that site of action with the

disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some totally different drug. There are for example, agents in antiviral and anticancer chemotherapy, which are not themselves effective, but are effective treatments when the agents are combined with something else. Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

It appears that the phrase "a pathological condition which is ameliorated by suppression of CD4+-T-cell-mediated immune response, other than a condition resulting from viral infection" is objected to in claim 29, because it is alleged to be unclear which pathological conditions fall within this phrase. Applicants respectfully traverse this rejection.

Applicants respectfully submit that one of ordinary skill in the art would appreciate the scope of the above phrase particularly in view of specific examples of such pathological conditions that are provided in the specification:
an autoimmune disorder, a chronic inflammatory disease, graft-versus host disease, transplant rejection, rheumatoid arthritis, type I-diabetes mellitus, autoimmune demyelinating diseases, multiple sclerosis, inflammatory bowel disease syndrome, psoriasis, discoid lupus erythematosus, systemic lupus erythematosus (SLE),adult respiratory distress syndrome, cardiovascular atherosclerosis, leukocytosis, and asthma. In view of what is know in the art concerning the etiology in general of disease conditions and in view of the number of examples provided, one of ordinary skill in the art would understand what pathological conditions are encompassed. Further, in view of the examples given one of ordinary skill in the art can assess whether or not a given pathological condition is associated with CD4+-T-cell-mediated immune response.

The Office Action states that the claim "does not set forth any steps involved in determining which are the disorders capable of being treated by ameliorated by

suppression of CD4+-T-cell-mediated immune response." Applicants submit that such steps are not required to practice the invention as claimed and the absence of such steps from the claims do not make the claims indefinite.

The specification in the paragraph bridging pages 1 and 2 states that;

> During the pathogenesis of autoimmune diseases, CD4+ T-cells contribute to inflammatory responses which result in joint and tissue destruction. These processes are facilitated by the recruitment of inflammatory cells of the hematopoietic lineage, production of antibodies, inflammatory cytokines and mediators, and by the activation of killer cells. Rheumatoid arthritis (RA) is one manifestation of an autoimmune phenomenon which results in erosion, deformity, and destruction of joints. RA is characterized by elevated levels of activated CD4+ T lymphocytes in the affected joints. Currently there is no cure for RA. CD4+ cells have also been implicated in other chronic conditions including psoriasis, insulin-dependent diabetes mellitus, systemic lupus erythematosus, inflammatory bowel diseases, multiple sclerosis and other autoimmune diseases. Accordingly, it is desirable to down-regulate the autodestructive activity of CD4+ cells in cases of autoimmune disorders without compromising normal host defenses against opportunistic infections.

This recitation indicates that it is appreciated and understood in the art that, CD4+ T-cells contribute to inflammatory responses and autoimmune diseases, including those listed. Applicants have demonstrated that the triaza compounds as claimed function to down-regulate CD4 expression in T cells (see Example 1 and Table 1). Applicants have further demonstrated that this down regulation is specific for CD4 compared to a variety of surface antigens (Table 2). Thus, in view of the data presented in the specification and in view of the understanding in the art that CD4+ T-cells contribute to inflammatory responses and autoimmune diseases, one of ordinary skill in the art would understand and appreciate that compounds of this invention are useful in the treatment of inflammatory and autoimmune diseases.

As further evidence that it is well-known in the art which pathological conditions are associated with CD4+-T cells and would be ameliorated by suppression of CD4+-T-cell-mediated immune response, Applicants refer to issued U.S. patent 6,562,343

issued in 2003 which is believed to represent the state of knowledge in the art at about the date of filing of the present application. In column 5, lines 45-63, this patent defined such disorders as:

> The TH cell subpopulation-related disorders described herein can include, for example, TH1 or TH1-like related disorders or can, alternatively, include TH2 or TH2-like related disorders. Examples of TH1 or TH1-like related disorders include chronic inflammatory diseases and disorders, such as Crohn's disease, reactive arthritis, including Lyme disease, insulin-dependent diabetes, organ-specific autoimmunity, including multiple sclerosis, Hashimoto's thyroiditis and Grave's disease, contact dermatitis, psoriasis, graft rejection, graft versus host disease and sarcoidosis. Examples of TH2 or TH2-like related disorders include atopic conditions, such as asthma and allergy, including allergic rhinitis, gastrointestinal allergies, including food allergies, eosinophilia, conjunctivitis, glomerular nephritis, certain pathogen susceptibilities such as helminthic (e.g., leishmaniasis) and certain viral infections, including HIV, and bacterial infections, including tuberculosis and lepromatous leprosy.

In view of the foregoing, which provide evidence that one of ordinary skill in the art would understand the meaning and scope of the term used in claim 29, this rejection should be withdrawn.

Claims 58-60 indicate particular pathological conditions which are ameliorated by suppression of CD4+-T-cell-mediated immune response and as such these claims as well as new claim 63 should be considered to be clear and definite with respect to this issue and should be considered patentable over this rejection.

The Office Action in paragraphs A-E above also refers to variations in drug efficacy, drug potency, dosage and dosage form and supposed requirements for drug combinations as factors which affect definiteness and clarity. Applicants do not understand how these issues relate to definiteness and clarity of the claim. It is unclear how the statement of paragraph C relates to the issue in question because claim 29 define the compounds useful for treatment in terms of a specific formula, not just any compound is claimed to be useful. Each of the listed paragraphs speculate on a

problem that might occur with any drug employed for any medical treatment and are not problems that are related to the specific language employed in the present claims. These statements also appear to imply that a patentee must establish details of the rate of efficacy, optimal dosage level and dosage form and rule out any other biological effects by the compounds whose use is claimed before a claim to their use is considered definite. Applicants are not aware that any of these details are needed to established definiteness and clarity of the claims herein. Both paragraphs D and E speculate that a certain problem may exist and then use this speculative problem as "evidence" of indefiniteness. There is no evidence presented on the record that such speculative problems would be encountered with the compounds whose use is claimed herein.

Applicants submit that none of the statements made in any of paragraphs A-E relate to the issue of definiteness and clarity of claim 29 and claims that depend there from.

In view of all the foregoing, this rejection should be withdrawn.

2. Claims 29-38, 40-42 and 58-60 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement. The Examiner refers to the requirement that the specification providing an enabling disclosure of how to make the invention.

The Office Action states:

> HOW TO MAKE: In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

> The nature of the invention in the instant case, has claims which embrace substituted triaza compounds. The instant compounds of the formulae wherein a, b, c and d are repeating groups for the carbon atom which they are associated with in addition to e which is associated with a variable in itself forms a wide ring of possible ring systems with the smallest possibility being a triazole on up. The magnitude of possible ring systems are not described in the disclosure in such a way the one of ordinary skill in the art would no (sic, know) how to prepare the various compounds suggested by claims 29-38, 40-42 and 58-60. For example where are the starting materials for the preparation of compounds where the triaza ring is a 1,4,7-triazacyclotetradecane ring.
>
> In view of the lack of direction provided in the specification regarding starting materials, the lack of working examples, and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention.

It appears that the major concern of the rejection is the scope of the variations in the ring systems of the compounds whose use is claimed. It is alleged that it would require undue experimentation for one of ordinary skill in the art to know how to prepare the various compounds of claims 29-38, 40-42 and 58-60. Applicants respectfully traverse this rejection.

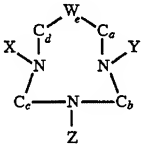
As a first matter, claim 29 has been amended to recite that the variables sum of the values of variables $a + d + e \geq 1$. This limitation requires that at least one of a, d or e is non-zero.

> In the specification at page 25, lines 8-12, the following description is provides:
>
> The synthesis of triaza compounds is described in U.S. Patents No.5,663,161, 6,342,492 and U.S. application serial no. 20002/0019423 published Feb. 14, 2002 the entirety of each of which is incorporated herein by reference. These methods along with methods provided herein and methods that are well-known in the art can be employed by one or ordinary skill in the art to synthesize the triaza compounds of this invention.

Applicants have incorporated the description of synthesis of triaza compounds disclosed in the listed US patents. As stated the description of these patents and published applications in combination with the synthetic examples provide in the present specification provide an enabling disclosure of how to make the triaza compounds whose use is claimed.

For example, claim 1 of issued U.S patent 5,663,161 recites:

1. A method of inhibiting a virus which comprises contacting the virus, a virus-infectable cell or a virus-infected cell with a compound of formula I:



wherein W is a bridge carbon which has a polar or non-polar side group;

X and Y independently are an aromatic group, an alkyl group, a sulfonyl group or a carbonyl group,

said aromatic group is selected from the group consisting of Ar, Ar sulfonyl, Ar carboxy and Ar alkyl, where Ar has from five to seven ring members and Ar is an aromatic cyclic or aromatic heterocyclic ring;

said alkyl groups having from one to ten carbons;

X and Y are not both an alkyl group;

Z is a group listed for X and Y, a fused aryl moiety having from seven to ten carbons or hydrogen;

a, d and e independently are a number from zero to 10 and when a, d and e are all zero, the compound of formula I is a non-cyclic triamine;

c and b independently are a number from one to ten; and the formula includes sufficient hydrogens for a stable molecule.

Presumably the '161 issued US patent provides an enabling disclosure of how to make the various triaza compounds whose uses are claimed therein. The compounds in claim 1 of the '161 patent are not as broad in scope as those of the present claim 29, but the variation in ring size defined by the variables a, b, c, d and e is substantially the same as in the claims of the present application. In fact, the claims herein as amended recite more restricted values for the variables a, d and e. Presumably this issued U.S. patent provides an enabling disclosure of how to make any and all of the ring size variations within the scope of its claim 1. The enabling disclosure of this issued patent has been incorporated by reference in its entirety in the present application and as such should be considered to provide an enabling disclosure at least of all compounds within the scope of claim 1 of the '161 patent. Further description is provided in the present specification for synthesis of additional triaza compounds for example in Example 4 and Scheme 1.

The Examiner alleges that starting materials for the synthesis of compounds of claim 29 have not been provided. Applicants submit that one of ordinary skill in the art of organic synthetic chemistry in view of descriptions in the specification and what is generally well-known in the art would know what starting materials are needed and would be able to obtain such starting materials from commercial sources or by synthetic methods that are well known in the art. The Examiner has asked "where are the starting materials for the preparation of compounds where the triaza ring is a 1,4,7-triazacyclotetradecane ring."

Applicants provide the following answer. Triaza macrocycles of this invention are synthesized employing the Richman-Atkins method which is well-known in the art. 1,4,7-triazacyclotetradecane derivatives can be synthesized using N,N-bis(2-tosylaminoethyl)tosylamide (see: T.J.Atkins, J.E.Richman, W.F.Oettle, Organic Syntheses, Vol. 58, pp 86-97; Organic Syntheses, Coll. Vol. VI, W.E.Noland (Ed.); Wiley, NY, 1988, 652-662, copy submitted herewith) and a dihalide or ditosylate (see:

F.Chavez, A.D.Sherry, J.Org.Chem., 1989, 54,2990-2992, copy submitted herewith). N,N',N"-tritosyl-1,4,7-triazacyclotetradecane can be prepared by reaction of bis(2-tosylaminoethyl)tosylamide with commercially available 1,7-dibromoheptane, or in one more steps from the ditosylate of commercially available heptane-1,7-diol. Thus, starting materials for making the a 1,4,7-triazacyclotetradecane can be made by methods described in the literature and/or are commercially available.

Applicants submit that the specification including descriptions incorporated by reference from U.S. Patents No.5,663,161, 6,342,492 and U.S. application serial no. 20002/0019423 published Feb. 14, 2002 provides an enabling disclosure of the compounds whose use is claimed in claim 29. Additionally, one of ordinary skill in the art in view of this description and what is well-known in the art can obtain starting materials as needed to prepare compounds as described in the specification herein. This is particularly the case for the ring size variants for values of a, b, c, e and d as claimed the synthesis of which is presumed to be enabled in U. S. patent 5,663,161.

The enablement requirement does not mandate that Applicants must disclose all of what is well known in the art. Indeed, as acknowledged in the Manual of Patent Examining Procedure (MPEP) at 2164.01, a patent need not teach, and preferably omits, what is well known in the art (citing In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987)).

In view of the forgoing this rejection should be withdrawn.

3. Claims 29-60 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement. The Office Action refers to the issue of how to use the invention. Applicants respectfully traverse this rejection.

The Office Action states:

HOW TO USE: Claims 29-60 are to "a method of treating an individual suffering from a pathological condition which is ameliorated by suppression of CD4+-T-cell mediated immune response". Any evidence presented must be commensurate in scope with the claims and must clearly demonstrate the effectiveness of the claimed compounds. However, the specification provides no definitive evidence to correlate any one disorder selected from those disclosed in the specification with the instantly disclosed triaza compounds.

No screening protocol(s) are ever described. Thus, no evidence of in vitro effectiveness is seen in the specification for one of the instantly claimed triaza compounds. In general, pharmacological activity is a very unpredictable area. In cases involving physiological activity "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). Since this case involves unpredictable in-vivo physiological activities, the scope of the enablement given in the disclosure presented here was found to be low.

The specification does not have working examples on the use of the substituted triaza compounds. The absence of working examples is one of the factors to be considered in deciding whether the practice of an invention would involve undue experimentation. There must be evidence to justify the contention that the claimed compounds can be useful in the treatment of "autoimmune disorder, chronic inflammatory disease, graft-versus host disease, transplant rejection, rheumatoid arthritis, type 1-diabetes mellitus, autoimmune demyelinating diseases such as multiple sclerosis, inflammatory bowel disease syndrome, psoriasis, discoid lupus erythematosus, systemic lupus erythematosus (SLE), adult respiratory distress syndrome, cardiovascular atherosclerosis, leukocytosis or asthma". Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied upon are reasonably predictive of in vivo efficacy by those skilled in the art, See In re Ruskin, 148 USPQ 221, Ex parte Jovanovics,21 1 USPQ 907, MPEP 2164.05(a).

Patent Protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute enabling disclosure. Genentech Inc. v. Novo Nordisk 42 USPQ2d 1001.

Contrary to the allegations of the Office Action, Applicants have demonstrated (see Examples 1 and 3) that compounds of this invention as exemplified by CADA and various additional compounds (30 compounds) of Table 5 specifically down-modulates CD4 expression. Applicants have thus shown that compounds of the invention function to cause a significant biological effect in cells, and more specifically in human T cells (two-types of human T cells as well as in PBM cells). Certain compounds of the invention were demonstrated to exhibit comparable results to anti-CD4 monoclonal antibodies. Additionally, cytotoxicity assays were conducted. These experiments represent working examples to assess the biological function of the compounds whose use is claimed herein.

Applicants submit that the CD4 downregulation assays are screening protocols for identifying compounds which are useful for treatment of autoimmune disorders and inflammation which are ameliorated by suppression of CD4+-T-cell-mediated immune response. Applicants further submit that the results of CD4 expression assays are evidence that the compounds tested are useful in the therapeutic methods as claimed.

The Examiner alleges that the utility claimed for the compounds herein "is unusual or difficult to treat or speculative" and as such that evidence that tests relied upon are reasonably predictive of in vivo efficacy by those skilled in the art can be required. Applicants submit as discussed above that the relationship between CD4+ T cells and inflammatory and autoimmune disorders is well-known in the art and as such Applicants stated utility in view of the assays performed is not unusual or speculative. The data presented support Applicants conclusions and assertions in the specification that the compounds of this invention have utility in the treatment of autoimmune disorders and inflammation.

The Office Action alleges that the practice of the invention as claimed requires undue experimentation. Applicants disagree. Certain additional experimentation may be required to practice the invention as long as that experimentation is not undue.

According to the MPEP at 2164.01:

> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

Applicants submit that the art routinely engages in experimentation to determine exact dosage and dosage forms for application of drug candidates in various disease conditions. This experimentation may be complex and may take a significant amount of time, but the methods for conducting such experimentation are well-known in the art and conducting such experiments does not amount to undue experimentation.

Because, Applicants have provided results of assays demonstrating a clear beneficial biological function (downregulation of CD4 expression) of compounds of this invention in human cells, and because that biological function is recognized in the art to be associated with certain pathological conditions, Applicants submit that they have provided a disclosure of how to use the compounds as claimed herein that would enable one of ordinary skill in the art to practice the invention as claimed without undue experimentation.

In view of the foregoing, this rejection should be withdrawn.

4. Claims 29-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Claim 29 has been amended to rewrite the definition of optional substitution. This definition contains the general definition that is provided in the specification on page 6, lines 1-16 as being substitution by one or more charged, polar or nonpolar

substituents with specific charged, polar and non-polar groups being further defined. Additionally, claim 29 contains the additional possible substituents for Ar groups that are listed in the specification at page 4, lines 18-25.

It is believed that the amendment of the claims obviates this rejection.

5. Claims 29-60 are rejected under 35 U.S.C. 102(a) as being anticipated by Bell et al. 15th International Conference on Antiviral Research. Applicants respectfully traverse this rejection.

The Bell et al. reference is the publication of a presentation made in March 2002 by Thomas W. Bell at the above referenced meeting. The present invention is a U.S. National Stage of a PCT application (PCT/US02/11223) filed April 8, 2002. This reference is a publication by the co-inventors of this application of their own work less than one year before the filing date of this application and as such is not available as prior art against this application.

The Bell et al. reference names co-inventors Thomas W. Bell, Dominique Schols, Kaka Dey and Kurt Vermeire as co-authors along with additional co-authors Q. Jin, E. Scarbrough, A. Sodoma, M.F. Samala and Erik De Clercq. Submitted herewith is the declaration of two of the co-inventors Thomas W. Bell and Dominique Schols providing evidence that co-authors Q. Jin, E. Scarbrough, A. Sodoma, M.F. Samala and Erik De Clercq are not co-inventors of the present application

This declaration explains that Thomas W. Bell was a Professor of Chemistry at the University of Nevada, Reno, at the time the invention was made and that all of K. Dey, Q. Jin, E. Scarbrough and A. Sodoma worked as graduate students under his direction. Prof. Bell declares that Q. Jin, E. Scarbrough, A. Sodoma and M.F. Samala were named as co-authors of the poster presentation noted above because each had synthesized compounds which were reported in the poster as having activity, but which

are not claimed in the present application. Prof. Bell also declares that co-inventor K. Dey was also named as a co-author because of this contribution to synthesis of compounds. But that in addition he is considered a co-inventor of this application because he contributed by synthesizing new compounds that were claimed in this application. Prof. Bell declares that none of the co-authors Q. Jin, E. Scarbrough, A. Sodoma or M.F. Samala, all of whom worked under his direction, contributed intellectually to the claims of the present application and none are believed to be co-inventors of the present application.

The declaration also explains that Dominique Schols was a Full-time Professor (Gewoon Hoogleraar) of the Faculty of Medicine, Rega Institute for Medical Research, Katholieke Universiteit Leuven, Belgium, at the time the invention was made. Prof. Schols declares that he was responsible for naming Erik De Clercq and Kurt Vermeire as co-authors of the poster presentation. Prof. Schols declares that co-author Eric De Clercq was at the time the poster was prepared and presented the Head of the Department of Microbiology and Immunology at the Rega Institute for Medical Research where the work leading to the poster presentation was performed. Prof. Schols indicates that it was customary to name Prof. De Clerq, the Department Head as a co-author on such presentations. Prof. Schols declares that Professor De Clercq did not contribute intellectually to any research that is reported in the poster presentation and is not believed to be a co-inventor of the above-referenced patent application. In contrast, Prof. Shols declares that co-author and co-inventor Kurt Vermeire, who worked under his direction, contributed intellectually to the subject matter of claims of the present application.

Because Prof. Bell and Prof. Schols directed the research leading to the invention and were responsible for naming co-authors on the poster, it is believed that they are in the best position to make the declaration explaining the naming of co-authors on the poster presentation.

In view of the declaration submitted, the cited reference represents a publication by the co-inventors of their own work less than one year prior to the filing of this application. The cited reference is thus not available as prior art to this application. This rejection should be withdrawn.

Conclusion

Applicants respectfully request reconsideration of the claims and withdrawal of the rejections. This response cancels two claims and adds three claims. It is believed that this submission requires payment of excess claims fees for one additional dependent claim, for which the fees (as a small entity) total $25.00. This response is accompanied by a Petition for Extension of Time of Three Months with fee in the amount of $510 (as a small entity). Please debit Deposit Account No. 07-1969 in the amount of $ 535 to pay the additional claims fee and extension of time fee. It this amount is incorrect, please debit any underpayment, or credit any overpayment, to Deposit Account No. 07-1969.

Respectfully submitted,

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Attorney docket no. 36-02
SAS:bds:March 30, 2007